

1 Point

# Clinical Applications of Misoprostol in Gynaecology

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This paper reviews the use of misoprostol in medical abortions, medical treatment of miscarriages and pre-operative preparations for various gynaecological procedures. Although there is good scientific evidence that misoprostol is safe and useful for these indications, these are off-label uses in many countries. Users should be familiar with the most updated information and recommendations regarding the appropriate regimens, and informed consent should be obtained

from the patients for the off-label use of misoprostol.

Misoprostol is an analogue of prostaglandin E1 (PGE1) which was initially licensed in many countries for the treatment of peptic ulcers in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) because of its gastric anti-secretory properties and its various mucosal protective properties.<sup>1</sup> In comparison to other prostaglandin (PG) analogues, misoprostol has the advantages of being

orally active, cheap, widely available, and stable at room temperature. These advantages are especially important in developing countries.

## UNIQUE PHARMACOLOGICAL PROPERTIES OF MISOPROSTOL

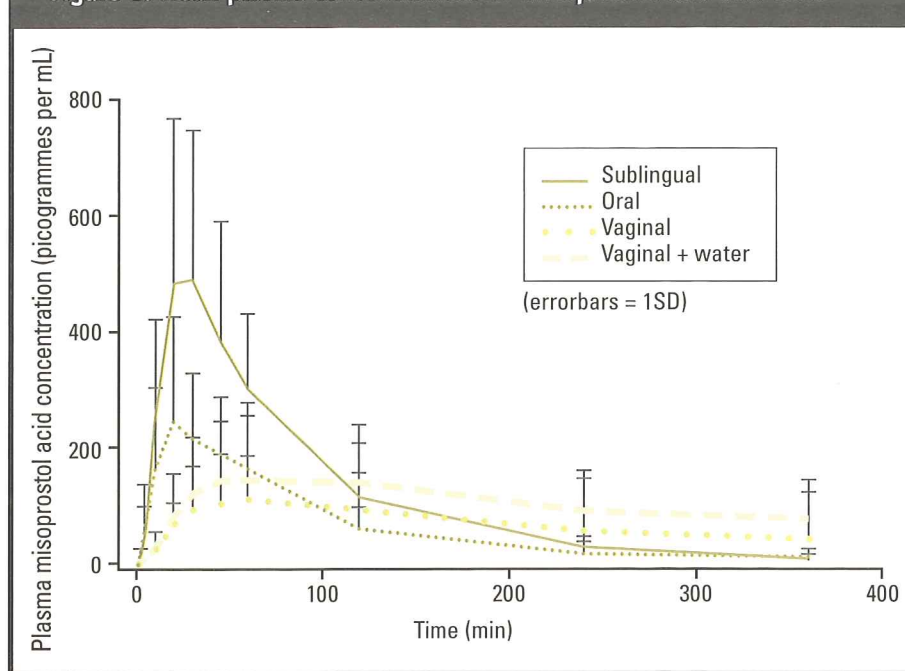
Although misoprostol was developed and licensed for oral administration, other routes of administration including vaginal, sublingual, buccal and rectal have been studied extensively in gynaecological applications. Figure 1 illustrates the pharmacokinetics of the different routes of misoprostol administration. Oral and sublingual administration have the quickest onset of action: the peak concentration is reached at about 30 minutes; it declines rapidly by 120 minutes and remains low thereafter. The sublingual route achieves the highest peak concentration and hence systemic bioavailability as measured by the area under the curve in the first 6 hours, and yet the side effects may be more frequent compared to other routes.

On the other hand, vaginal absorption is slower, and a lower peak serum misoprostol concentration than that of the other routes is reached in 70–80



Misoprostol has been gaining wide applications in gynaecology.

**Figure 1. Mean plasma concentrations of misoprostol acid over time**



minutes after administration, but the drug level is sustained for a longer period of time beyond 6 hours after a single dose, which hence confers a higher overall bioavailability suitable for indications that require a longer clinical action, eg, medical abortion.

Vaginal absorption of misoprostol is inconsistent, and remnants of tablets are sometimes seen many hours after administration. For vaginal administration, no significant difference in bioavailability has been demonstrated between dry tablets and the tablets moistened with water, although the latter is a common practice.<sup>2</sup>

Other routes of administration, such as the buccal and rectal routes, have also been explored. It appears that the serum concentration profiles for buccal and rectal routes are similar to that of vaginal

administration but at a lower level.<sup>3</sup>

Misoprostol is generally a safe and well-tolerated drug. Common side effects include fever, chills, gastrointestinal upset and diarrhoea. The fever is transient and can be controlled with anti-pyretics. The gastrointestinal side effects are usually self limiting. If necessary, NSAIDs can be used for controlling abdominal cramps without affecting the effectiveness of misoprostol.<sup>4,5</sup> When misoprostol is used for its uterotonic property, uterine rupture is a rare though serious risk. It should be noted that multiple congenital defects, most notably the Mobius Syndrome involving the central nervous system and limbs, have been reported with exposure to misoprostol in early pregnancy. This is probably due to a disturbed blood supply to the developing embryo rather than a direct teratogenic effect. It is estimated

that the absolute risk of fetal malformation after misoprostol exposure is low, around the order of 1%.<sup>6</sup> Contraindications for the use of misoprostol include known allergy to the drug, suspected ectopic pregnancy, haemodynamic instability and septic abortion. Despite the common misconception, asthma is not a contraindication for misoprostol use.

## MEDICAL ABORTION IN THE FIRST TRIMESTER

The combination of mifepristone, an antiprogesterone, followed by a PG analogue 24–48 hours later, has become an established gold standard for termination of pregnancy in the first trimester. Misoprostol is a preferred PG analogue for this purpose since it is relatively cheap and is stable at room temperature. It has been shown that vaginal misoprostol is more effective and has a lower incidence of side effects than oral misoprostol when combined with mifepristone in medical abortion, achieving a complete abortion rate of over 95%.<sup>7</sup> If a woman cannot accept vaginal administration of misoprostol, the sublingual route may be used, as both the sublingual and vaginal routes have similar abortion rates, though the sublingual route produces a higher incidence of side effects.<sup>8</sup> A recent World Health Organisation (WHO) study revealed that a 24-hour interval between mifepristone and misoprostol was as effective as a 48-hour interval in terms of complete abortion rate.<sup>9</sup>

Although mifepristone is highly



effective in inducing abortion when combined with PG, it is not available in many countries, mainly because of political concerns in marketing it as an abortion drug. Therefore, the use of PG alone in medical abortion has been extensively studied. Various misoprostol-only regimens have been investigated, and a simple comparison of their effectiveness is not possible due to non-uniformity in many variables including dosage, interval between doses, gestational age and criteria in defining treatment outcome. Most published reports were on vaginal administration of multiple doses of 800 mcg of misoprostol, in up to three doses at 6, 12 or 24 hour intervals, and the complete abortion rate varied between 60–90%.<sup>10</sup> The available information suggests that effectiveness is dose-related up to 800 mcg with the vaginal route.<sup>11</sup>

When misoprostol is used alone, the vaginal route is more effective than the oral route<sup>12</sup> and should be the route of choice. When the vaginal route is not preferred by the woman, sublingual administration at 3-hour intervals is a reasonable alternative, which is similar in effectiveness to the vaginal route, but causes more frequent side effects.<sup>10</sup> Expulsion of the conception product occurs in about 80% and 95% of cases by 24 and 48 hours post-administration. When used in medical abortion up to 9 weeks, pregnancy continues in 4–8% of cases. Women with incomplete abortion can be offered the options of surgical evacuation or repeat treatment with 600 mcg of oral misoprostol.<sup>13</sup> The patient should

<b>Indication</b>	<b>Recommended regime</b>	<b>Remarks</b>
Induced abortion in first trimester (up to 9 weeks)	With mifepristone: mifepristone 200 mg orally followed 1–3 days later by misoprostol 800 mcg vaginally (can repeat another dose in 4 hours if needed)  Without mifepristone: 800 mcg vaginally 12-hourly x 3	Complete abortion rate: >95% with mifepristone, 60–90% without mifepristone
Induced abortion in second trimester (13–20 weeks)	With mifepristone: mifepristone 200 mg orally followed 36–48 hours later by misoprostol 800 mcg vaginally then 400 mcg orally 3-hourly x 4 maximally  Without mifepristone: 400 mcg vaginally 3-hourly x 5 maximally  Can repeat course or consider alternatives if fail.	Complete abortion rate: 97% within 24 hours with mifepristone; 80–90% within 24 hours without mifepristone
Miscarriages	Silent miscarriage: 800 mcg vaginal or 600 mcg sublingual (can repeat in 3 hours if needed)  Incomplete abortion: 600 mcg orally or vaginally (single dose)	Complete abortion rate 60–90% depending on criteria of defining “completeness”  Intervention not recommended within 2 weeks unless heavy bleeding or infection.
Cervical priming pre-instrumentation	400 mcg vaginally 3 hours before procedure	For surgical abortion, dilatation and curettage, hysteroscopy
Prior to myomectomy	400 mcg vaginally 1 hour before operation	For reducing operative blood loss

be counselled about the possibility of treatment failure, and should be prepared to terminate the pregnancy by surgical means because there have been reports of congenital malformations in misoprostol-exposed babies, as described above.

Most studies report the use of misoprostol for up to 9 weeks of gestation. Some studies suggest that the combination of mifepristone with misoprostol is also effective in medical abortion at between 10–12 weeks of gestation. However, more

**Table 2. Meta-analysis on the pre-treatment with misoprostol prior to hysteroscopy in premenopausal women.<sup>27</sup>**

Outcome	Number of studies	Misoprostol (%)	Control (%)	Relative Risk (95% CI)	P-value
Need for further dilatation	3	60/141 (42.6%)	104/145 (71.7%)	0.61 (0.51 – 0.73)	<0.001
Cervical laceration	5	4/196 (2.0%)	20/181 (11.0%)	0.22 (0.09 – 0.56)	0.001
Uterine perforation / false passage	4	2/150 (1.3%)	4/136 (2.9%)	0.39 (0.08 – 1.85)	0.24
Nausea	3	7/141 (5.0%)	1/145 (0.7%)	5.23 (0.92 – 29.65)	0.06
Diarrhoea	3	6/141 (4.3%)	0/145 (0.0%)	7.20 (0.90 – 57.56)	0.06
Vaginal bleeding	2	26/119 (21.8%)	2/124 (1.6%)	11.09 (3.08 – 40.00)	0.0002
Abdominal cramping	2	41/119 (34.5%)	5/124 (4.0%)	7.98 (3.38 – 18.84)	<0.0001
Fever	3	12/141 (8.5%)	2/145 (1.4%)	5.24 (1.37 – 20.09)	0.02

studies are required before definitive recommendations can be made.

## MEDICAL ABORTION IN THE SECOND TRIMESTER

The medical method for second trimester induced-abortions recommended by the WHO and the Royal College of Obstetricians and Gynaecologists (RCOG) is the regimen of mifepristone followed by a PG analogue.<sup>14,15</sup> This combined regimen results in a significantly shorter induction-to-abortion interval than when PG is used alone. Vaginal administration of misoprostol is more effective than

other routes, and the incidence of side effects is lower.<sup>16</sup> However, more women prefer the oral route to the vaginal route as the former is more convenient, less uncomfortable and less embarrassing. When mifepristone is available, 200 mg of mifepristone is given orally, followed by 800 mcg of vaginal misoprostol 36–48 hours later, and then 400 mcg of oral misoprostol is administered every 3 hours for up to 4 doses or till expulsion of the conceptus.<sup>17</sup> If mifepristone is not available, misoprostol can be used alone: 400 mcg of vaginal misoprostol given 3-hourly at up to 5 doses is an effective regimen.<sup>17, 18</sup> The dose can be deferred in the presence of strong regular uterine contractions. With

the combined mifepristone-misoprostol regimen, the median induction-abortion interval is about 6 hours, and 97% of women will abort within 24 hours. With the misoprostol-alone regimen, the median induction-abortion interval is 10–15 hours and 80–90% of the women will abort within 24 hours. If abortion fails within 24 hours after the first dose of misoprostol and there is no significant side effect, a second course can be commenced at least 12 hours after the last dose. If abortion still fails, an alternative PG, oxytocin infusion and surgical dilatation and evacuation could be the next option.<sup>17</sup> When terminating pregnancies after 20 weeks, intra-amniotic digoxin or fetal intracardiac potassium chloride injection should be considered as the fetus may show signs of life after abortion. Because of the potential for heavy vaginal bleeding and more serious complications, it is advisable to conduct second trimester terminations in the hospital, where facilities for transfusion and surgical operation are available.

## CERVICAL PRIMING BEFORE SURGICAL ABORTION

When the abortion is performed by vacuum aspiration, misoprostol is also useful in pre-operative cervical dilatation. A multicenter study by the WHO showed that the use of PG before vacuum aspiration can reduce intraoperative blood loss, risk of re-curettage, and readmission due to infection or abnormal bleeding.<sup>19</sup> Vaginal and sublingual misoprostol have similar efficacy for this purpose but the



sublingual route produces more side effects.<sup>20</sup> Some studies found that vaginal misoprostol is more effective than the oral route, whereas others did not show a difference. The recommended regimen is 400 mcg of vaginal, oral or sublingual misoprostol 3 hours pre-operatively.<sup>21</sup> There is no recommendation on whether pre-operative cervical priming should be administered routinely to all surgical abortions, but this may be particularly useful in late first trimester abortions, nulliparous women, and other situations when difficulty in cervical dilatation is anticipated. The regimen for cervical priming prior to dilatation and evacuation for second trimester abortions is less well defined.

## MEDICAL MANAGEMENT OF MISCARRIAGE

There are three options for the management of miscarriages: surgical, medical and expectant. Misoprostol has been extensively studied for medical treatment of miscarriages which offers an alternative to avoid the risks of surgery. It is believed that mifepristone may not be necessary for this purpose as the progesterone level in a non-viable pregnancy is already low, and it has been shown in a randomized trial that the addition of mifepristone did not improve the overall success rate compared to misoprostol-alone regimens.<sup>22</sup> A meta-analysis has shown that medical management was 2.8-fold more likely to induce complete miscarriage than expectant management.<sup>23</sup>

The best regimen is yet to be defined, as all existing reported studies are largely heterogeneous in the outcome indicator for successful treatment.

It should be noted that complete miscarriage should not be expected immediately after the administration of medication, in contrast to surgical evacuation, and the timing in defining treatment success or failure would affect the reported "success rate", which has ranged from 60 to 90%. The success rate of medical management for incomplete miscarriage would be higher compared to silent miscarriage.<sup>24</sup> One of the recommended regimens is 800 mcg of vaginal misoprostol as a single dose for silent miscarriage, and 600 mcg of vaginal misoprostol for incomplete miscarriage; additional doses can be administered if the conceptus is not expelled over a certain period of observation.<sup>24</sup> Although the single dose regimen has been mostly recommended, an alternate approach is to give repeated doses over one day. One reported regimen by our group was to give 600 mcg misoprostol either vaginally or sublingually 3-hourly for a maximum of three doses. This achieved a complete abortion rate of 87.5%.<sup>25</sup>

Despite the avoidance of potential surgical complications such as infection, cervical and uterine injury and Asherman's syndrome, medical treatment is associated with a higher incidence of gastrointestinal upsets, abdominal pain, and prolonged heavy bleeding. Therefore, the relative pros and cons should be explained to help the patient in making an informed choice. Expulsion of the gestational product and

the associated bleeding can take up to several weeks to complete. It is advisable to arrange a follow-up visit after 7–14 days to review the patient by symptoms and signs. "Failed medical evacuation" should not be over-diagnosed. A decision for surgical completion should be based on clinical condition rather than on sonographic feature, and is not generally recommended within the initial 7 days unless there is heavy bleeding or clinical sign of infection.<sup>13</sup>

## PRE-OPERATIVE CERVICAL DILATATION OF THE NON-PREGNANT CERVIX

Misoprostol is also effective in priming the cervix in non-pregnant women before transcervical procedures, and our group has conducted the first trial on this, demonstrating a significant reduction in cumulative force required for cervical dilatation.<sup>26</sup> A meta-analysis showed that in pre-menopausal women, misoprostol before hysteroscopy resulted in significantly reduced need for further mechanical dilatation, a lower rate of cervical laceration, and yet higher rate of PG-related side effects including vaginal bleeding, cramping and fever (Table 2).<sup>27</sup>

In most studies, 400 mcg of vaginal misoprostol about 12 hours pre-operative were used.<sup>21</sup> One study reported that 400 mcg of oral misoprostol had similar efficacy as 200 mcg of vaginal misoprostol.<sup>28</sup> The results in post-menopausal women, however, are conflicting.<sup>29,30</sup> Potentially, the use of misoprostol priming may

also enhance insertion of intrauterine contraceptive devices, and in reducing complications on cervical procedures in patients with tight os or those previously subjected to cone biopsy, although there is currently no well-conducted clinical trial on these scenarios.

### CERVICAL PRIMING BEFORE COLPOSCOPY

Misoprostol may be useful in unsatisfactory colposcopy. In a randomized placebo-controlled trial in patients with unsatisfactory colposcopy where the transformation zone or abnormal lesion is not entirely visualized, the administration of 400 mcg of vaginal misoprostol 6 hours before repeat colposcopy enabled a satisfactory colposcopic examination in 78.9% of patients compared to the placebo group (30%,  $p=0.004$ ).<sup>31</sup> A recent case report also suggested that administration of 100 mcg oral misoprostol one night before colposcopy in an adolescent

girl with cervical stenosis resulted in a satisfactory colposcopic examination and biopsy.<sup>32</sup>

### REDUCTION OF OPERATIVE BLOOD LOSS IN GYNAECOLOGICAL OPERATIONS

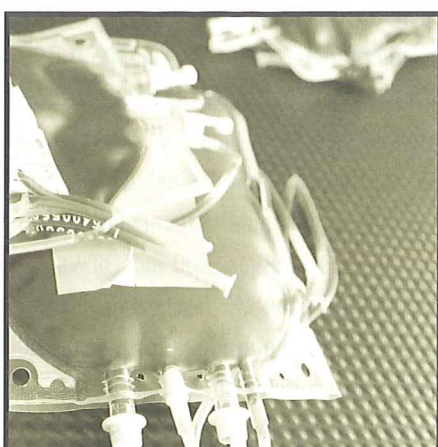
There may be other potential applications of misoprostol in pre-operative preparation in gynaecological operations. A placebo-controlled trial in patients undergoing

myomectomy showed that 400 mcg of vaginal misoprostol given 1 hour pre-operatively significantly reduced the blood loss, operative time and need for post-operative transfusion.<sup>33</sup> This may theoretically result from the effect of misoprostol in enhancing myometrial contraction as well as vasoconstriction.

There is currently limited data to conclude on the value of pre-operative misoprostol in hysterectomies. One study showed that a combination of intravenous oxytocin and rectal misoprostol in laparoscopic-assisted vaginal hysterectomy

#### SUMMARY OF IMPORTANT POINTS

1. Misoprostol is a PGE1 analogue. It has the unique properties of being cheap, orally active, easily accessible and stable at room temperature.
2. The sublingual route achieves the highest systemic bioavailability in the first 6 hours but side effects may be more frequent; the vaginal route achieves a slower and lower peak serum level which sustains for a longer time and hence a higher overall bioavailability.
3. Common side effects include gastrointestinal upset, diarrhoea, fever and chills. Association with congenital CNS and limb defects is possible with fetal exposure in the first trimester.
4. The combination of mifepristone and vaginal misoprostol is the regimen of choice for termination of pregnancy in the first trimester (up to 9 weeks of gestation), with a success rate of over 95%. The sublingual route can also be used, although side effects are more frequent.
5. Vaginal misoprostol alone can be used for first trimester medical abortions but the complete abortion rate is lower, which ranges between 60 and 90%.
6. Multiple doses of vaginal misoprostol, either in combination with mifepristone or used alone, can be used to terminate second trimester pregnancies.
7. Vaginal misoprostol alone can be used in medical treatment of miscarriages, with a success rate of 60–90%.
8. Vaginal misoprostol can effectively prime both the pregnant and non-pregnant cervix before surgical procedures which require cervical dilatation.
9. Pre-operative misoprostol may help in reducing operative blood loss in myomectomy; its role in hysterectomy needs to be investigated further.



Oxytocin and misoprostol may reduce blood loss in laparoscopic-assisted vaginal hysterectomy.



significantly reduced the blood loss, operative time, change in haemoglobin level and duration of hospitalization.<sup>34</sup> Our recent randomized controlled trial, however, revealed that the administration of 400 mcg of sublingual misoprostol 1 hour before abdominal hysterectomy for symptomatic fibroids did not have any significant difference in blood loss compared with those receiving placebo (Chai *et al*, unpublished data).

## CONCLUSIONS

The current gynaecological applications of misoprostol—a prostaglandin with unique properties and diverse off-label uses—are reviewed in this paper. Misoprostol has been found to be valuable in medical abortions, management of miscarriages, and as pre-operative adjuncts in various gynaecological procedures. As all these applications are not the licensed

indications, it is of utmost importance for the clinician to be familiar with the updated evidence-based recommendations regarding the appropriate regimens, and to obtain informed consent from the patients before using misoprostol for these off-label indications.

## About the Author

Dr Li is an Associate Consultant in the Department of Obstetrics and Gynaecology at the Queen Mary Hospital, Hong Kong.

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1 Point

## Clinical Applications of Misoprostol in Gynaecology

Answer True or False to the questions below.

	True	False
1. Common side effects of misoprostol include abdominal cramps, diarrhoea, fever and chills, which are transient and self-limiting.	<input type="radio"/>	<input type="radio"/>
2. Apart from its original indication as an anti-ulcer agent, misoprostol has a wide range of registered uses in gynaecology, including medical abortion, management of miscarriage and pre-treatment before various gynaecological procedures.	<input type="radio"/>	<input type="radio"/>
3. Compared to other routes of administration, the serum misoprostol level is maintained for a longer time after vaginal administration; hence the vaginal route is more effective for medical abortions.	<input type="radio"/>	<input type="radio"/>
4. Wetting the misoprostol tablet before vaginal administration enhances its bioavailability compared to using the dry tablet.	<input type="radio"/>	<input type="radio"/>
5. The combination of mifepristone and vaginal misoprostol has a better efficacy in inducing abortion in the first trimester compared to vaginal misoprostol alone.	<input type="radio"/>	<input type="radio"/>
6. Multiple doses of misoprostol are usually required to induce second trimester abortions.	<input type="radio"/>	<input type="radio"/>
7. For cervical priming, misoprostol should be given one hour before surgical abortion procedures in order to achieve the best efficacy.	<input type="radio"/>	<input type="radio"/>
8. In medical management of miscarriage by misoprostol, an ultrasound scan should be repeated within 2 to 3 days after administration of the drug, and any suspected retained product should be evacuated surgically as soon as possible.	<input type="radio"/>	<input type="radio"/>
9. In contrast to the pregnant state, misoprostol is not effective in pre-operative cervical dilatation before transcervical procedures in non-pregnant women.	<input type="radio"/>	<input type="radio"/>
10. There is some evidence that pre-operative misoprostol administration can reduce the blood loss in myomectomy.	<input type="radio"/>	<input type="radio"/>

Name in BLOCK CAPITALS: \_\_\_\_\_

Signature: \_\_\_\_\_

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1	2	3	4	5	6	7	8	9	10
F	T	T	F	T	T	T	F	F	T